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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,539	ABE ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *3,4 and 7-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/28/06 and 10/3/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendices A and B*.

DETAILED ACTION

Status of the Application

[1] Claims 1-33 are pending in the application.

Election/Restriction

[2] Applicants' election without traverse of Group I, claims 1-2 and 5-6, in the reply filed on 3/11/09, is acknowledged.

[3] Claims 3-4 and 7-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 3/11/09.

Claim for Foreign Priority

[4] This application is a 371 national stage filing of PCT/JP2005/001068, filed on 1/27/05, which claims foreign priority under 35 USC § 119(a)-(d) to JP 2004-019251, filed on 1/28/04. A certified copy of the foreign priority document in a non-English language has been filed in this application on 7/28/06.

Information Disclosure Statement

[5] All documents cited in the information disclosure statements filed on 7/28/06 and 10/3/07 have been considered by the examiner. A copy of Forms PTO/SB/08 is attached to the instant Office action.

Specification/Informalities

[6] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: ---Neoculin Acidic Subunit, A Taste-Modifying Polypeptide---.

[7] The abstract of the disclosure is objected to because it is not a single paragraph. Correction is required. See MPEP § 608.01(b).

[8] The substitute specification filed on 7/28/06 is objected to because, while a clean copy has been filed, there is no marked-up version as required by 37 CFR 1.125(c).

Claim Objection

[9] 1-2 and 5-6 are objected to in the recitation of the abbreviations "NAS", "NBS", and "PNAS". Abbreviations, unless otherwise obvious and/or commonly used in the art, *e.g.,* "DNA", should not be recited in the claims without at least once reciting the entire phrase for which the noted abbreviations are used. Appropriate correction is required.

[10] Claims 1 and 5 are objected to as reciting the improper sequence identifier "SEQ ID NO.2", "SEQ ID NO.6", and "SEQ ID NO.3", which should be replaced with "SEQ ID NO:2", "SEQ ID NO:6", and "SEQ ID NO:3", respectively. See 37 CFR 1.821(d).

[11] Claim 5 is objected to in the recitation of "which polypeptide grows to the mature polypeptide NAS via processing" and in the interest of improving claim form, it is suggested that the noted phrase be amended to recite, "which polypeptide is processed to the mature polypeptide NAS".

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[12] Claims 1-2 and 5-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 1 (claim 2 dependent therefrom) and 5 (claim 6 dependent therefrom) recites the limitation "the neoculin dimer". There is insufficient antecedent basis for this limitation in the claim.

[b] Claims 1 (claim 2 dependent therefrom) and 5 (claim 6 dependent therefrom) are indefinite in the recitation of “which polypeptide” in line 6 of claim 1 and line 6 of claim 5 because it is unclear as to the polypeptide that is referenced by the noted phrase – the polypeptide of (A), the polypeptide of (B), or the polypeptide of (A) and (B). See also the phrase “which polypeptide” in line 13 of claim 1 and line 14 of claim 5. It is suggested that applicant clarify the meaning of the noted phrase. In the interest of advancing prosecution and giving claims their broadest reasonable interpretation, the phrase “which polypeptide” in line 6 of claim 1 and line 6 of claim 5 is interpreted as referencing only part (B).

[c] Claim 5 (claim 6 dependent therefrom) is indefinite in the recitation of the limitation “grows to the mature polypeptide NAS via processing” because it is unclear as

to the scope of polypeptides that is intended as being encompassed by "the mature polypeptide NAS". Also, there is insufficient antecedent basis for the limitation “the mature polypeptide NAS” in the claim.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

[13] Claims 1-2 and 5-6 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to a polypeptide. The claims read on a product of nature and should be amended to indicate the hand of the inventor, e.g., by insertion of “purified” or “isolated”. See MPEP § 2105.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[14] Claim(s) 1-2 and 5-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 1 is drawn to a genus of neoculin acidic subunit (NAS) polypeptides comprising: (A) an amino acid sequence of SEQ ID NO:2 or (B) an amino acid sequence with the substitution, deletion, insertion, addition or inversion of one or several amino acids in SEQ ID NO:2, which polypeptide can form the neoculin dimer having a taste-modifying activity together with a genus of neoculin acidic subunit (NBS) polypeptides comprising: (a) an amino acid sequence shown in SEQ ID NO:6 in the sequence listing or (b) an amino acid sequence with the substitution, deletion, insertion, addition or inversion of one or several amino acids in SEQ ID NO:6, which polypeptide can be a subunit constituting curculin.

Claim 5 is drawn to a genus of precursor neoculin acidic subunit (PNAS) polypeptides comprising: (A) an amino acid sequence of SEQ ID NO:3 or (B) an amino acid sequence with the substitution, deletion, insertion, addition or inversion of one or several amino acids in SEQ ID NO:3, which polypeptide is processed to a mature NAS polypeptide to be able to form the neoculin dimer having a taste-modifying activity together with a genus of neoculin acidic subunit (NBS) polypeptides comprising: (a) an amino acid sequence shown in SEQ ID NO:6 in the sequence listing or (b) an amino acid sequence with the substitution, deletion, insertion, addition or inversion of one or several amino acids in SEQ ID NO:6, which polypeptide can be a subunit constituting curculin.

Claims 2 and 6 are limit the genus of polypeptides of claims 1 and 5 to being glycosylated with an N-linked sugar chain comprising mannose/N-acetylglucosamine/fucose/xylose at a ratio of 3/2/1/1.

In view of the recitation of the grammatically indefinite article "an", the phrase "an amino acid sequence" in (A), (B), (a), and (b) is broadly and reasonably interpreted as any two contiguous amino acids of SEQ ID NO:2. The recitation of "NAS" in the preamble of claims 1-2 and "PNAS" in the preamble of claims 5-6 is given no patentable weight and thus the claims encompass *any* polypeptide that comprises two or more contiguous amino acids of SEQ ID NO:2 or 3.

Also, it is noted that the counterpart to (A) and (B) to form a “neoculin dimer” as recited in (a) and (b) is also structurally and functionally unlimited.

MPEP 2163.II.A.2.(a).i) states, “Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention”. For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.,* structure or other physical

and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 further states that a "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In this case, the specification discloses an actual reduction to practice of a single representative species of the genus of NAS and PNAS proteins as encompassed by the claims, *i.e.,* SEQ ID NO:2 and 3, respectively. Other than these species, the specification fails to disclose any other species of the genus of recited NAS or PNAS polypeptides as encompassed by the claims by complete or partial structure, drawings, or chemical formula. Also, there is no art-recognized correlation between the function of SEQ ID NO:2 or 3 and its corresponding amino acid sequence. It is well known that the amino acid sequence and resulting conformation of a polypeptide determines its function. The level of knowledge and skill in the art does not allow those skilled in the art to structurally envisage or recognize those structures of variants of SEQ ID NO:2 or 3 that result in a polypeptide that can form a neoculin dimer with SEQ ID NO:6 and that maintains a sweet taste because it is known that the function of polypeptides will tend to differ unpredictably based on their amino acid sequences. Other than the two representative species as noted above, the specification fails to describe any changes to SEQ ID NO:2 and 3 that can be made with an expectation of achieving neoculin

dimer formation. No common structural attributes identify the members of the substitution, deletion and insertion variant genus. Because the disclosure fails to describe the common attributes or characteristics that identify substitution, deletion and insertion variant members of the genus, and because the genus is highly variant, the two disclosed representative species are insufficient to describe the genus, even when considered in light of the general knowledge in the art concerning amino acid modification(s).

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus, and thus, that the applicant was not in possession of the recited genus. The claimed subject matter is not supported by an adequate written description because a representative number of species has not been described.

[15] Claims 1-2 and 5-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide comprising SEQ ID NO:2 or 3, optionally glycosylated with an N-linked sugar chain comprising mannose/N-acetylglucosamine/fucose/xylose at a ratio of 3/2/1/1 when the polypeptide is purified from the fruit of *Curculigo latifolia* plant, does not reasonably provide enablement for all polypeptides as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

"The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: Claim 1 is drawn to a genus of neoculin acidic subunit (NAS) polypeptides comprising: (A) an amino acid sequence of SEQ ID NO:2 or (B) an amino acid sequence with the substitution, deletion, insertion, addition or inversion of one or several amino acids in SEQ ID NO:2, which polypeptide can form the neoculin dimer having a taste-modifying activity together with a genus of neoculin acidic subunit (NBS) polypeptides comprising: (a) an amino acid sequence shown in SEQ ID NO:6 in the sequence listing or (b) an amino acid sequence with the substitution, deletion, insertion, addition or inversion of one or several amino acids in SEQ ID NO:6, which polypeptide can be a subunit constituting curculin.

Claim 5 is drawn to a genus of precursor neoculin acidic subunit (PNAS) polypeptides comprising: (A) an amino acid sequence of SEQ ID NO:3 or (B) an amino

acid sequence with the substitution, deletion, insertion, addition or inversion of one or several amino acids in SEQ ID NO:3, which polypeptide is processed to a mature NAS polypeptide to be able to form the neoculin dimer having a taste-modifying activity together with a genus of neoculin acidic subunit (NBS) polypeptides comprising: (a) an amino acid sequence shown in SEQ ID NO:6 in the sequence listing or (b) an amino acid sequence with the substitution, deletion, insertion, addition or inversion of one or several amino acids in SEQ ID NO:6, which polypeptide can be a subunit constituting curculin.

Claims 2 and 6 are limit the genus of polypeptides of claims 1 and 5 to being glycosylated with an N-linked sugar chain comprising mannose/N-acetylglucosamine/fucose/xylose at a ratio of 3/2/1/1.

In view of the recitation of the grammatically indefinite article "an", the phrase "an amino acid sequence" in (A), (B), (a), and (b) is broadly and reasonably interpreted as any two contiguous amino acids of SEQ ID NO:2. The recitation of "NAS" in the preamble of claims 1-2 and "PNAS" in the preamble of claims 5-6 is given no patentable weight and thus the claims encompass *any* polypeptide that comprises two or more contiguous amino acids of SEQ ID NO:2 or 3.

Also, it is noted that the counterpart to (A) and (B) to form a “neoculin dimer” as recited in (a) and (b) is also structurally and functionally unlimited.

The amount of direction provided by the inventor; The existence of working examples: The specification discloses a single working example of an NAS polypeptide that is able to combine with SEQ ID NO:6 to form a neoculin subunit and that maintain a

sweet taste and taste modifying effect, *i.e.,* SEQ ID NO:2, and a single working example of a PNAS polypeptide, *i.e.,* SEQ ID NO:3, which is processed to SEQ ID NO:2. However, these working examples, in combination with the remaining disclosure of the specification fail to provide the necessary guidance for making the entire scope of claimed polypeptides as noted above. Also, the specification fails to provide guidance for using those polypeptides that do not maintain the activity of forming a dimer with SEQ ID NO:6 and that maintain a sweet taste.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The amino acid sequence of a polypeptide determines the polypeptide's structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.*, expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.,* multiple substitutions.

It is well-known in the art that even a single amino acid alteration can alter the function of a polypeptide. See, *e.g.,* MPEP 2144.08.II.A.4.(c), which states, "[i]n the area

of biotechnology, an exemplified species may differ from a claimed species by a conservative substitution ("the replacement in a protein of one amino acid by another, chemically similar, amino acid... [which] is generally expected to lead to either no change or only a small change in the properties of the protein." Dictionary of Biochemistry and Molecular Biology 97 (John Wiley & Sons, 2d ed. 1989)). The effect of a conservative substitution on protein function depends on the nature of the substitution and its location in the chain. Although at some locations a conservative substitution may be benign, in some proteins only one amino acid is allowed at a given position. For example, the gain or loss of even one methyl group can destabilize the structure if close packing is required in the interior of domains. James Darnell et al., Molecular Cell Biology 51 (2d ed. 1990)."

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of isolating or generating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen for any and all polypeptide variants as encompassed by the claims.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use all polypeptides as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated

with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

[16] Claim(s) 1-2 and 5-6 are rejected under 35 U.S.C. 102(a) as being anticipated by Suzuki et al. (“Recombinant curculin heterodimer exhibits, taste-modifying and sweet-tasting activities”, *FEBS Lett.* 573:135-138, 2004; cited in the IDS filed on 7/28/06; hereafter "Suzuki”) OR Shirasuka et al. (“Neoculin as a New Taste-modifying Protein Occurring in the Fruit of *Curculigo latifolia*”, *Biosci. Biotechnol. Biochem.* 68:1403-1407, 2004; cited in the IDS filed on 7/28/06; hereafter " Shirasuka”).

The reference of Suzuki discloses a curculin isoform, referred to as “curculin2”, present in a preparation of a curculin fraction from the pulp of *Curculigo latifolia* (p. 135, column 2, middle). The amino acid sequence of curculin2 (p. 136, Figure 1) is 100%

identical to SEQ ID NO:2 herein (see Appendix B sequence alignment). According to the specification, the polypeptide isolated from the fruit of *C. latifolia* is glycosylated with an N-linked sugar chain comprising mannose/N-acetylglucosamine/fucose/xylose at a ratio of 3/2/1/1 (p. 41) and thus because curculin2 of Suzuki is isolated from the fruit of *C. latifolia,* it is necessarily glycosylated with an N-linked sugar chain comprising mannose/N-acetylglucosamine/fucose/xylose at a ratio of 3/2/1/1. This anticipates claims 1-2 and 5-6 as written.

The reference of Shirasuka discloses "neoculin", present in a preparation of an extract of the fruit of *Curculigo latifolia* (p. 1403, columns 1-2), which is a heterodimer with an acidic subunit called NAS and a basic subunit called NBS. The amino acid sequence of NAS (p. 1404, Figure 1 and p. 1405, Figure 2) is 100% identical to SEQ ID NO:2 and 3 herein (see Appendix B sequence alignment). As noted above, according to the specification, the polypeptide isolated from the fruit of *C. latifolia* is glycosylated with an N-linked sugar chain comprising mannose/N-acetylglucosamine/fucose/xylose at a ratio of 3/2/1/1 (p. 41) and thus because NAS of Shirasuka is isolated from the fruit of *C. latifolia,* it is necessarily glycosylated with an N-linked sugar chain comprising mannose/N-acetylglucosamine/fucose/xylose at a ratio of 3/2/1/1. This anticipates claims 1-2 and 5-6 as written.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[17] Claim(s) 1-2 and 5-6 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Yamashita et al. (Purification and Complete Amino Acid Sequence of a New Type of Sweet Protein with Taste-modifying Activity, Curculin", *J. Biol. Chem.* 265:15770-15775, 1990; hereafter "Yamashita"; cited in the IDS filed on 7/28/06) as evidenced by Suzuki (*supra*) and Shimizu-Ibuka et al. (*J. Mol. Biol.* 359:148-158, 2006; hereafter referred to as "Shimizu-Ibuka"). See MPEP 2112.III regarding a rejection under 35 U.S.C. 102/103 and see MPEP 2131.01 regarding a multiple reference 35 U.S.C. 102 rejection.

The reference of Yamashita teaches an extract of *Curculigo latifolia* fruit that is sweet and comprises curculin (p. 15570, column 1).

That the curculin of Yamashita comprises a polypeptide encompassed by claims 1-2 and 5-6 is shown by the evidentiary references of Suzuki and Shimizu-Ibuka. Suzuki

discloses that the only active form of curculin from the fruit of *Curculigo latifolia* is a heterodimer of curculin1 and curculin2 (which correspond to NBS and NAS, respectively), where only the curculin1-2 heterodimer exhibits sweet-tasting and taste-modifying activities (p. 136, column 2). As noted above, the amino acid sequence of curculin2 is 100% identical to SEQ ID NO:2 herein. Shimizu-Ibuka teaches "Curculin, occurring in the fruit of *Curculigo latifolia*…was initially regarded as a homodimer consisting of two identical subunits, although the recombinant homodimer was devoid of any taste-modifying activity. A recent study revealed that the active component is actually a heterodimeric protein, which was designated as 'neoculin'. This protein consists of an acidic, glycosylated subunit (neoculin acidic subunit, NAS) of 113 amino acid residues…" As noted above, according to the specification, the polypeptide isolated from the fruit of *C. latifolia* is glycosylated with an N-linked sugar chain comprising mannose/N-acetylglucosamine/fucose/xylose at a ratio of 3/2/1/1 (p. 41) and thus because curculin of Yamashita is isolated from the fruit of *C. latifolia,* it is necessarily glycosylated with an N-linked sugar chain comprising mannose/N-acetylglucosamine/fucose/xylose at a ratio of 3/2/1/1.

This anticipates claims 1-2 and 5-6 as written.

Conclusion

[18] Status of the claims:

Claims 1-33 are pending.

Claims 3-4 and 7-33 are withdrawn from consideration.

Claims 1-2 and 5-6 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656

APPENDIX A: Alignment of SEQ ID NO:2 and SEQ ID NO:3

Query sequence 1

>SEQ ID NO:2
DSVLLSGQTLYAGHSLTSGSYTLTIQNNCNLVKYQHGRQIWASDTDGQGSQCRLTLRSDG
NLIIYDDNNMVVWGSDCWGNNGTYALVLQQDGLFVIYGPVLWPLGLNGCRSLN

Query sequence 2

>SEQ ID NO:3
MAAKFLLTILVTFAAVASLGMADSVLLSGQTLYAGHSLTSGSYTLTIQNNCNLVKYQHGR
QIWASDTDGQGSQCRLTLRSDGNLIIYDDNNMVVWGSDCWGNNGTYALVLQQDGLFVIYG
PVLWPLGLNGCRSLNGEITVAKDSTEPQHEDIKMVINN

Full-length alignment between two sequences

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>>SEQ ID NO:3                                              (158 aa)
 s-w opt: 791  Z-score: 983.8  bits: 187.7 E(): 5.5e-53
Smith-Waterman score: 791;  100.000% identity (100.000% ungapped) in 113 aa overlap (1-113:23-
135)

                                    10        20        30
SEQ                           DSVLLSGQTLYAGHSLTSGSYTLTIQNNCNLVKYQHGR
                              :::::::::::::::::::::::::::::::::::::::
SEQ    MAAKFLLTILVTFAAVASLGMADSVLLSGQTLYAGHSLTSGSYTLTIQNNCNLVKYQHGR
              10        20        30        40        50        60

       40        50        60        70        80        90
SEQ    QIWASDTDGQGSQCRLTLRSDGNLIIYDDNNMVVWGSDCWGNNGTYALVLQQDGLFVIYG
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
SEQ    QIWASDTDGQGSQCRLTLRSDGNLIIYDDNNMVVWGSDCWGNNGTYALVLQQDGLFVIYG
              70        80        90       100       110       120

      100       110
SEQ    PVLWPLGLNGCRSLN
       :::::::::::::::
SEQ    PVLWPLGLNGCRSLNGEITVAKDSTEPQHEDIKMVINN
```

APPENDIX B

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CURC2_CURLA
ID   CURC2_CURLA             Reviewed;         158 AA.
AC   Q6F495; Q3MV17;
DT   03-MAR-2009, integrated into UniProtKB/Swiss-Prot.
DT   16-AUG-2004, sequence version 1.
DT   16-JUN-2009, entry version 20.
DE   RecName: Full=Curculin-2;
DE   AltName: Full=Neoculin acidic subunit;
DE            Short=NAS;
DE   Flags: Precursor;
OS   Curculigo latifolia (Lumbah).
OC   Eukaryota; Viridiplantae; Streptophyta; Embryophyta; Tracheophyta;
OC   Spermatophyta; Magnoliophyta; Liliopsida; Asparagales; Hypoxidaceae;
OC   Curculigo.
OX   NCBI_TaxID=4676;
RN   [1]
RP   NUCLEOTIDE SEQUENCE [MRNA], PROTEIN SEQUENCE OF 23-135, AND VARIANT
RP   ASN-80.
RX   PubMed=15215616; DOI=10.1271/bbb.68.1403;
RA   Shirasuka Y., Nakajima K., Asakura T., Yamashita H., Yamamoto A.,
RA   Hata S., Nagata S., Abo M., Sorimachi H., Abe K.;
RT   "Neoculin as a new taste-modifying protein occurring in the fruit of
RT   Curculigo latifolia.";
RL   Biosci. Biotechnol. Biochem. 68:1403-1407(2004).
RN   [2]
RP   NUCLEOTIDE SEQUENCE [MRNA], AND DISULFIDE BONDS.
RX   PubMed=15327988; DOI=10.1016/j.febslet.2004.07.073;
RA   Suzuki M., Kurimoto E., Nirasawa S., Masuda Y., Hori K., Kurihara Y.,
RA   Shimba N., Kawai M., Suzuki E., Kato K.;
RT   "Recombinant curculin heterodimer exhibits taste-modifying and sweet-
RT   tasting activities.";
RL   FEBS Lett. 573:135-138(2004).
RN   [3]
RP   X-RAY CRYSTALLOGRAPHY (2.76 ANGSTROMS) OF 23-135, SUBUNIT, AND
RP   DISULFIDE BONDS.
RX   PubMed=16616933; DOI=10.1016/j.jmb.2006.03.030;
RA   Shimizu-Ibuka A., Morita Y., Terada T., Asakura T., Nakajima K.,
RA   Iwata S., Misaka T., Sorimachi H., Arai S., Abe K.;
RT   "Crystal structure of neoculin: insights into its sweetness and taste-
RT   modifying activity.";
RL   J. Mol. Biol. 359:148-158(2006).
CC   -!- FUNCTION: Taste-modifying protein; sweet-tasting. After curculin,
CC       water elicits a sweet taste, and sour substances induce a stronger
CC       sense of sweetness.
CC   -!- SUBUNIT: Heterodimer with curculin-1; Disulfide-linked.
CC   -!- SIMILARITY: Contains 1 bulb-type lectin domain.
CC   ---------------------------------------------------------------------
CC   Copyrighted by the UniProt Consortium, see http://www.uniprot.org/terms
CC   Distributed under the Creative Commons Attribution-NoDerivs License
CC   ---------------------------------------------------------------------
DR   EMBL; AB167079; BAD29946.1; -; mRNA.
DR   EMBL; AB167080; BAE45253.1; ALT_INIT; mRNA.
DR   EMBL; AB181490; BAD38841.1; -; mRNA.
DR   PDB; 2D04; X-ray; 2.76 A; A/C/E/G=23-135.
DR   PDBsum; 2D04; -.
DR   SMR; Q6F495; 23-133.
DR   GO; GO:0005529; F:sugar binding; IEA:UniProtKB-KW.
DR   InterPro; IPR001480; B_lectin_man_bd.
DR   Pfam; PF01453; B_lectin; 1.
DR   SMART; SM00108; B_lectin; 1.
DR   PROSITE; PS50927; BULB_LECTIN; 1.
PE   1: Evidence at protein level;
KW   3D-structure; Direct protein sequencing; Disulfide bond; Glycoprotein;
KW   Lectin; Polymorphism; Signal; Taste-modifying protein.
FT   SIGNAL        1     22
FT   CHAIN        23    135       Curculin-2.
FT                                 /FTId=PRO_0000366212.
FT   PROPEP      136    158
FT                                 /FTId=PRO_0000366213.
```

```
FT   DOMAIN       23    131       Bulb-type lectin.
FT   CARBOHYD    103    103       N-linked (GlcNAc. . .) (Potential).
FT   DISULFID     51     74
FT   DISULFID     99     99       Interchain (with C-131 in NBS).
FT   DISULFID    131    131       Interchain (with C-99 in NBS).
FT   VARIANT      80     80       S -> N.
SQ   SEQUENCE   158 AA;  17174 MW;  CE597B53F069FFE1 CRC64;

  Query Match             100.0%;  Score 619;  DB 1;  Length 158;
  Best Local Similarity   100.0%;
  Matches  113;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 DSVLLSGQTLYAGHSLTSGSYTLTIQNNCNLVKYQHGRQIWASDTDGQGSQCRLTLRSDG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         23 DSVLLSGQTLYAGHSLTSGSYTLTIQNNCNLVKYQHGRQIWASDTDGQGSQCRLTLRSDG 82

Qy         61 NLIIYDDNNMVVWGSDCWGNNGTYALVLQQDGLFVIYGPVLWPLGLNGCRSLN 113
              |||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         83 NLIIYDDNNMVVWGSDCWGNNGTYALVLQQDGLFVIYGPVLWPLGLNGCRSLN 135
```